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EXAMINER	
KAUFMAN, CLAIRE M	
ART UNIT	PAPER NUMBER
1646	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/579,088	DURRANI ET AL.	
	Examiner	Art Unit	
	CLAIRE KAUFMAN	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 March 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-18,28-32 and 69-71* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-18,28-32 and 69-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/18/09,10/9/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

The rejection of claims 1-12, 19-27 and 33-68 are moot in view of the cancelation of the claims.

The rejection of claims 28-30 under 35 USC 112, second paragraph, as being duplicate claims is withdrawn in view of the cancellation of the corresponding duplicate claims. Claims 28 and 30 remain rejected under 35 USC 112, second paragraph, as described below.

The rejection of claims 19, 20, 22, 28-30 under 35 U.S.C. 102(b) as being anticipated by US 5,618,786 (IDS filed 1/14/08) is withdrawn in view of the cancellation of or amendment the claims.

The rejection of claims 1-7, 10-12, and 28-30 under 35 U.S.C. 102(b) as being anticipated by US 6,267,958) is withdrawn in view of the cancellation or amendment of the claims.

The rejection of claims 8-9, 13-27 and 31-32 under 35 U.S.C. 103(a) as being unpatentable over US 6,267,958 as applied to claims 1-7, 10-12, and 28-30 above, and further in view of US 5,166,134 (IDS filed 1/14/08) is withdrawn in view of the cancellation or amendment of the claims; however, a new rejection appears below addressing the amendments to the claims.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 28 and 30 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the reasons set forth in the previous Office action.

Claims 28 and 30 remain unclear because of the use of the terms "native" and "variant'. While the specification says that ""native AAT" (alpha 1-antitrypsin) refers to AAT forms that can be isolated from natural sources" (p. 4, lines 19-20 [0020], variant AAT refers to functional equivalents to the native (p. 4, line 34) and "proteins that are substantially identical to a native

sequence." (p. 5, line 6) Also, native AAT includes allelic and splice variants as well as truncated forms (p. 4, lines 21-22). Because of the overlap in definitions, the metes and bounds of variant vs. native AAT cannot be determined.

Applicants argue that "AAT" refers to proteins having the native AAT sequence as well as variants, with "native" defined as "isolated from natural sources" (p. 4, lines 19-20 of specification). A subgenus of the AAT proteins are variants which are "functional equivalents to" [0021] native AAT, but not themselves native AAT proteins. The argument has been fully considered, but is not persuasive. It is unclear how one can distinguish by sequence or even function which proteins are "native" and which are "variant". Additionally, the specification does not actually exclude native AATs from "AAT variants". The variants are only defined as being "functional equivalents to native sequence AAT proteins having similar amino acid sequences and retaining one or more activities of native AAT" (p. 4, lines 34-36). Again, it comes down to being able to distinguish a native AAT from a variant AAT. While it might be clear in some cases which is which, there is sufficient ambiguity and breadth in the definition of variant AAT so the metes and bounds of terms cannot be sufficiently determined.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13-18, 28-32 and 69-71 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an AAT which is a serine protease inhibitor, does not reasonably provide enablement for an AAT which does not have serine protease inhibitory activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for the reasons set forth in the previous Office action.

The claims are drawn to a pharmaceutical composition comprising an AAT, which is a native, recombinant or variant AAT, in addition to other non-protein components. Because the composition is a "pharmaceutical composition", it must have therapeutic use. Wildtype AAT is recognized as a serine proteinase (or protease) inhibitor (US 5,166,134, col. 2, lines 4-25, IDS of 1/14/08). There is no structural or functional limitation of the AAT in the claims. That is, the AAT is not claimed by specific sequence, for example, which would inherently confer a particular function or have an explicit functional requirement. It is acknowledged that there are over 100 AAT naturally occurring genetic variants known (Luisetti et al., Thorax, 59:164-9, 2004). However, the claims including an "AAT variants" include not only functional variants, but sequence variants with substitutions, deletions and/or insertions relative to a native sequence (which includes allelic and splice variants). Single amino acid changes effect the function of AAT. Van Steenbergen (Acta Clin. Belgica, 43:171, 1993) reports (paragraph beginning p. 176, col. 2) that substitution of Glu342 -> Lys342 results in a deficiency variant in which "85% of the normally synthesized polypeptide is blocked in the endoplasmic reticulum…." "Glu264 -> Val264 …does not lead to intracellular accumulation but to an early intracellular proteolysis…." This is pharmacologically important because mutation of these residue can lead to significantly decreased plasma levels and increased risk of emphysema and liver disease (*ibid.).* Carrell et al. (Nature, 1982, IDS filed 1/14/08) showed that two AAT variants are linked to progressive loss of lung elasticity that contributes to lung damage such as emphysema (*e.g.*, p. 33, col. 2, second paragraph).

Native variants have been characterized as "normal, deficient, null and dysfunctional" (Ljujic et al., J. Biochem. Biophys. Meth. 68(3):167-173, 2006, p. 168, end of second full paragraph). Because one skilled in the art would not reasonably expect that an AAT which was not a proteinase inhibitor could be of therapeutic benefit, and because the claims encompass an AAT with no or reduced serine protease inhibitor function, the invention is not enabled for the full breadth of the claims. That is, an AAT with reduced activity compared to the normal wildtype AAT would be expected to increase a subject's risk of lung and/or liver disease and the specification has not taught how to therapeutically use such AAT molecules.

Applicants argue that the claims have been amended to obviate the rejection by specifying that the AAT is "functional". The argument has been fully considered, but is not persuasive. According the specification in [0021], "AAT activities include, but are not limited to, capacity to inhibit elastase, cathepsin G and/or proteinase 3. Other exemplary AAT activities include capacity to inhibit degranulation of lung mast cells, to inhibit histamine release factors, to inhibit the release of tumor necrosis factor (TNF) and/or to inhibit the release of leukotriene B4 from alveolar macrophages and cells." These are exemplary activities. Further, an AAT with a greatly reduced ability to, for example, inhibit elastase compared to wildtype AAT would not reasonably be expected to be of pharmaceutical benefit. The claims are not limited to those which provide a therapeutic advantage. Nor are the claims drawn to a method of, for example, inhibiting elastase. They are simply drawn to a "pharmaceutical composition". In order for such a composition to be enabled, it must have a therapeutic use. Many, perhaps even most, of the "functional" AATs encompassed by the claims would not reasonably be expected to. Therefore, the inventors have not taught how to use the invention commensurate in scope with the claims.

Applicants list court cases which support that the need for further experimentation does not mean the invention is not enabled, but only if the experimentation is undue. Also, that which is well known is preferable omitted from an application. While the facts of these cases are acknowledged by the Examiner, it is maintained that undue experimentation would be required in the instant situation. As discussed in the previous Office action, native variants have been characterized as normal, deficient and null, with these terms referring only to the level of AAT detected in plasma. This does not necessarily relate to AAT function or the individual's health. Further, Luisetti et al., published after the effective filing date of the instant application, (Thorax, 59:164, Feb. 2004, see PTO-892 of 8/27/09, p. 169, end of first paragraph of col. 2) note that, "Clinical phenotypes associated with the common AAT deficient variant PI*Z are reasonably well define, but no information is so far available on clinical phenotypes associated with rare AAT deficient variants. This should be addressed by future studies." While native mutant forms of AAT have been identified, their activity has not necessarily been identified. Knowing a compound's activity is critical when it is the active ingredient of a pharmaceutical composition. Further, because the claims encompass endless variants that have some type and level of function, identifying them and sufficiently understanding not only their sequence but their

physiological activity would require undue experimentation in view of the sheer number of compounds encompassed by the claims, the breadth of the claims as they relate to a "functional alpha 1-antitrypsin", the limited knowledge in the prior art about the function of less common native variants and possible function of non-native variants, the lack of working examples of pharmaceutical efficacy except for one functional AAT, and the paucity of guidance or direction concerning making or identifying functional AATs that the skilled artisan would reasonably expect to be effective in a pharmaceutical composition, it is maintained that it would require undue experimentation to make the claimed invention commensurate in scope with the claims.

Applicants argue that, "Specific examples of native AAT sequences are available from GenBank as well as the patent literature." Recombinant and suitable variant AAT proteins have been described. The specification also describes well known methods for making and testing variants, as well as provides evidence of exemplary AAT sequences. The argument has been fully considered, but is not persuasive. Many of the nonpatent and US patent references filed by Applicants in the IDS of 10/9/09 deal with recombinant protein production by yeast. Many of the foreign references deal with metalloproteinase. Even though references such as Schasteen et al. (Mole. Immunol, 28:17, 1991, IDS filed 10/9/2009) which discusses C-terminal amino acid substitutions that produce functionally equivalent serine proteases including AAT, they are not sufficient to support enablement of the full scope of the invention which is any AAT variant with a function that can be used pharmaceutically. Not only have a commensurate number of therapeutically beneficial AAT variants not been made or generally described so the skilled artisan could reasonably predict which sequences would have the necessary property, but neither the specification nor the prior art have taught how to use in a pharmaceutical composition those "functional AAT" proteins with, for example, significantly reduced activity compared to wildtype AAT or which have an extremely reduced plasma half-life.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 13-18, 28-32 and 69-71 are rejected under 35 U.S.C. 103(a) as being unpatentable over 5,618,786 (IDS filed 1/14/08) and US 6,267,958 (PTO-892 mailed 8/27/09) in view of US 6,653,284 (attached hereto) and US 5,166,134 (IDS filed 1/14/08).

US 5,618,786 teaches an aerosol formulation in which recombinant AAT (col. 4, lines 16-17) is in an amount to provide 1μg to 10mg/kg of host or 0.1-15 weight % of formulation, though "the amount employed will vary depending upon a number of factors, including the size of the particle, frequency of administration, nature of the disease, whether the treatment is for therapeutic or prophylactic purposes, etc." (col. 3, lines 5-7 and 25-31). Also included may be lactose (a carbohydrate; col. 3, line 10 and 16-17) and a surfactant (*e.g.*, a diglyceride) (col. 3, lines 10-18). The AAT is used "to inhibit elastase, a proteolytic enzyme affecting lung tissue and implicated as a major cause of emphysema" (col. 2, lines 21-24). The AAT may be purified or recombinant (*e.g.*, claim 9). US 5,618,786 does not teach the glycosylation state of the AAT, or the inclusion of an antioxidant in the formulation. Concentrations of 0.01-0.5% w/v of surfactant and 1-5% w/v of carbohydrate are not explicitly taught.

US 6,267,958 teaches a generally applicable pharmaceutical composition comprising a protein, exemplified by HER-2 antibody, but which may be AAT, wherein the composition may be lyophilized or aqueous and the protein is at a concentration in aqueous formulation at about 5-50 mg/ml (col. 6, lines 49, and col. 17, lines 5-15). Included in the composition may be a carbohydrate, called a "lyoprotectant", such as trehalose (col. 9, lines 21-25), a surfactant such as polysorbate 80 present at about 0.001-0.5% (col. 15, lines 36-59) and an antioxidant such as methionine (col. 16, lines 5-9). The lypoprotectant enables the protein to essentially retain its physical and chemical stability and integrity upon lyophylization and storage (col. 9, lines 36-38). The composition is also taught reconstituted with a diluent, which includes water (*e.g.,* col.

2, lines 20-23). It is noted that (col. 17, lines 55-61), "The appropriate dosage ("therapeutically effective amount") of the protein will depend, for example, on the condition to be treated, the severity and course of the condition, whether the protein is administered for preventive or therapeutic purposes, previous therapy, the patient's clinical history and response to the protein, the type of protein used, and the discretion of the attending physician." Further (col. 10, lines 12-17), "The protein to be formulated is prepared using techniques which are well established in the art including synthetic techniques (such as recombinant techniques and peptide synthesis or a combination of these techniques) or may be isolated from an endogenous source of the protein."

US 6,653,284 teaches a pharmaceutical formulation for keratinocyte growth factor-2 (KGF-2) which comprises an antioxidant such as methionine at about 0.1-2% w/v (¶[59] and claim 69) or ascorbic acid at about 0.01-2% w/v, a surfactant such as polysorbate 80 at about 0.003-0.02% ([59]), and a carbohydrate such as sucrose or trehalose at about 0.01-5% w/v (claims 41 and 57).

US 5,166,134 teaches AAT in an aqueous pharmaceutical formulation wherein the AAT is 0.1 to 4.5% by weight of the solution (col. 2, lines 58-61) and is in combination with an antioxidant such as vitamin E and a carbohydrate such as sorbitol (col. 4, lines 22-27 and Example 2). The AAT may be in a glycosylated or nonglycosylated recombinant form (col. 3, lines 17-19). AAT is reported to be especially useful because of its association with elastase and kinins. (col. 3, lines36-37). It is stated that (col. 3, lines 44-46), "The recombinant gene product of the invention is especially useful since it is free of contaminating viruses when produced." "Serine protease inhibitors such as α_1-antitrypsin and α_1-antichymotrypsin have been found to be useful in the treatment of dermatitis by inhibition and/or binding with elastase, cathepsin G and human mast cell chymase." (col. 1, lines 57-61) Application by inhalation to the lung is taught (*e.g.*, col. 4, lines 43-51).

It would have been obvious at the time the invention was made to one of ordinary skill in the art to have a pharmaceutical preparation of AAT as a powder, as taught for aerosolization by US 5,618,786 or for lyphilization for storage by US 6,267,958, or aqueous form as taught by US 5,166,134. AAT was known to inhibit elastase (see US 5,618,786 and US 5,166,134) and have therapeutic benefit. As stated in US 5,618,786, the AAT may be purified (native) or recombinat. The amount of AAT present depends on many factors including route and frequency of

administration, nature of disease, use as therapeutic or prophylactic, etc., as discussed by US 5,618,786 and US 6,267,958. It would have been obvious and desirable to include a carbohydrate/lycoprotectant such as trehalose, antioxidant such as methionine and surfactant for their old and well known stabilization and lung tissue penetration properties, respectively. If further would have been routine optimization to determine favorable formulation concentrations of the different components based on the guidance in the pharmaceutical prior art, such as a surfactant in the range of 0.001-0.5% w/v (*e.g.,* US 6,267,958), an antioxidant in the range of 0.1-2% w/v (*e.g.,* US 6,653,284), carbohydrate in the range of 0.01-5% w/v (*e.g.,* US 6,653,284) and AAT in the range of 1-10 mg/kg or 0.1-15% w/v (*e.g.,* US 5,618,786). It further would have been obvious to use native, recombinant or variant AAT since the meets and bounds of the AATs overlap and use would reasonably depend on availability of source and/or target subject. Similarly, whether the AAT is glycosylated or not (see, *e.g.*, US 5,166,134) would reasonably be expected to depend on its source and desirability of using either type since it was old and well known how to obtain glycosylated or unglycosylated proteins.

Prior Art

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Levine et al. (BioPharm, 5(4):36-40, 1992) discuss the advantages of using trehalose for lyophilization/dehydration of cells, solutions and foods. They note its well known ability to protect proteins against denaturation (p. 38, middle of last paragraph).

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire Kaufman, whose telephone number is (571) 272-0873. Dr. Kaufman can generally be reached Monday, Tuesday, Thursday and Friday from 9:30AM to 2:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached at (571) 272-0835.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Official papers filed by fax should be directed to (571) 273-8300. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Claire Kaufman, Ph.D.

/Claire Kaufman/

Patent Examiner, Art Unit 1646

July 1, 2010

/Gary B. Nickol /

Supervisory Patent Examiner, Art Unit 1646